FAST TRACK ARTICLE

Community Exposure to Perfluorooctanoate: Relationships Between Serum Levels and Certain Health Parameters

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Objective: The objective of this study was to determine whether certain biomarkers of toxicity and/or a past diagnosis of liver or thyroid disease were associated with serum perfluorooctanoate concentrations (PFOA) in a community with longstanding environmental exposure to PFOA. Methods: Serum (PFOA), hematologic and biochemical biomarkers, and a questionnaire were administered to 371 residents selected by stratified random sampling and a lottery among volunteers. Median PFOA was 354 ng/mL (interquartile range, 181–571 ng/mL). Results: No significant positive relationships between serum (PFOA) and liver or renal function tests, cholesterol, thyroid-stimulating hormone, or with red cell indices, white cell, or platelet counts. Mean serum (PFOA) was not increased in those with a history of liver or thyroid disease. Conclusions: No toxicity from PFOA was demonstrated using the measured end points; other end points need to be addressed. (J Occup Environ Med. *2006;48: 771–779*)

Perfluorooctanoate (PFOA, CF_3, $[CF_2]_6$ $C00^-$, CAS No. 3825-26-1) is a persistent pollutant in the environment and found at low concentrations in many diverse human populations globally. PFOA has defined toxicity to experimental species, but the toxicity to humans remains unclear. In this article, we report the first published study of possible health effects of PFOA in a nonoccupational group.

PFOA has commercial use primarily as ammonium perfluorooctanoate, an essential surface-active agent in the production of various fluoropolymers, including tetrafluoroethylene. Fluoropolymers are used in a wide variety of industrial and consumer products, including non-stick cookware, waterproof, breathable textiles, consumer house wares, electronics, aerospace, and other applications. PFOA also occurs as a contaminant in other fluorochemicals and telomer products.[1] Telomers are highly fluorinated compounds used in protective coatings for carpets, paper, construction materials, and apparel, and in insecticide formulations and high performance surfactant products. PFOA is not detectable in fluoropolymer cookware samples studied under simulated cooking conditions.[2] Ammonium perfluorooctanoate is fully dissociated into the anion form, perfluorooctanoate, in environmental media and biologic fluids.

PFOA is a manmade chemical with no known natural source[3] that is persistent in the environment and is resistant to biologic, environmental, or photochemical degradation. PFOA,

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along with a related compound, perfluorooctane sulfonate (PFOS), is now found both in marine animals inhabiting widely spread geographic biospheres[4] and in human serum from widely disparate groups. The median serum PFOA concentration ([PFOA]) in the U.S. population is around 4 to 5 μg/L with occasional values above 20 μg/L.[5–7]

The toxicology of PFOA has recently been reviewed.[1,8] In rats, PFOA is well absorbed after both oral and inhalation exposure[9,10] distributing primarily to the liver, plasma, and kidneys.[11] PFOA binds covalently to proteins in the rat liver, plasma, and testes.[11] The serum half-life in rodents is a few days with slower elimination in male rats than female.[12,13] Urine and feces are the principal routes of excretion in male rats; urine only in females[14] and castrated male rats.[14,15] In male rats, fecal excretion of PFOA is increased by cholestyramine resin intake, suggesting enterohepatic circulation.[16]

PFOA is not metabolized in mammals.[9,12,17] A number of toxic effects have been observed in experimental species. PFOA is one of a group of compounds that activates the peroxisome proliferator activated receptor (PPAR) alpha in rats leading to a response characterized broadly as peroxisomal proliferation.[1] In rats, PFOA is strongly hepatotoxic[10,18]; male rats are more susceptible.[19] Aged rats are also more susceptible to the liver damage and oxidative stress caused by PFOA.[20] PFOA is immunotoxic to rats, resulting in a decrease in spleen and thymus weights[21] as a result of both PPAR alpha-dependent processes[22] and actions mediated through the brain.[23] PFOA has been associated with increased serum estradiol and reduced testosterone in rats possibly due to induction of hepatic aromatase activity.[24]

Monkeys fed PFOA show decreased thyroid hormone levels, increases in liver weight and toxic hepatic changes,[25] slight to moderate hypocellularity of the bone marrow, moderate atrophy of lymphoid follicles, and marked diffuse lipid depletion in the adrenals.[19]

Carcinogenesis studies in rats fed PFOA show statistically significant increases in liver tumors, pancreatic acinar cell tumors, testicular Leydig cell adenomas (males), and mammary hyperplasia (females) compared with controls.[26,27] In rodents, PFOA promotes liver carcinogenesis.[28–30] Although the significance of these tumors to humans is unclear, the International Agency for Research on Cancer[31] has concluded that liver tumors induced in rodents by PPAR agents are unlikely to be operative in humans based on the current understanding of the mode of action in animals. Although tumor formation by PFOA was thought to occur only through nongenotoxic mechanisms,[32] Yao and Zhou[33] have recently reported that PFOA exerts genotoxic effects on human hepatoma HepG2 cells mediated through intracellular reactive oxygen species and oxidative DNA damage.

Because of profound differences in PFOA half-lives between species, toxicokinetics of PFOA in humans cannot be predicted based on animal data.[8] The half-life in the blood of PFOA in rats, after a single oral dose, was 4 hours in females and 9 days in males.[12] In rabbits, the serum half-life is in the order of 4 hours for both males and females.[34] The serum half-life in cynomolgus monkeys is approximately 20 days with urine as the primary source of excretion.[35,36] The mean half-life in the serum of human retirees from the 3M Company who had previous heavy occupational exposure was 4.37 years (range, 1.5–13.49 years; standard deviation, 3.53) without substantial gender differences. Age, body mass index (BMI), and number of years since retirement were not significant predictors of the human serum half-lives in multivariate regression analysis.[37] In humans, the renal clearance of PFOA is 10^{-5} fold less than the glomerular filtration rate suggesting the absence of excretion by human kidneys.[38] Thus, the published half-life in human females is approximately 35,000 times longer than that for the female rat.

Human studies addressing potential PFOA toxicity are limited. Cross-sectional analysis of routine medical surveillance results from facilities producing both PFOA and PFOS have found significant positive association between serum PFOA and increased cholesterol, triglycerides, and thyroid hormone (T3) levels.[39] Cross-sectional studies of hormonal levels in workers at a PFOA production facility have found significant associations between serum hormones and PFOA in some years[40] but not other years.[41] Elevated serum liver enzymes were associated with occupational exposure to PFOA but only in obese men (BMI >35 kg/m^2)[42] and not in subsequent years.[43] Preliminary results from two recent unpublished studies of workers occupationally exposed to PFOA have also observed a positive association between serum (PFOA) and serum cholesterol (Dupont Company, personal communication).

A retrospective cohort mortality study at a plant producing PFOA found an elevated standardized mortality ratio for prostate cancer in chemical production workers, which was significantly associated with length of employment in chemical production. The relative risk of prostate cancer was 3.3 (95% confidence interval, 1.02–10.6) for workers employed in chemical manufacturing for 10 years or more.[44] A follow-up study in which workers were classified into multiple exposure groups did not confirm the association,[45] but may have been limited by low statistical power to detect elevation in cancer rates in the smaller, reclassified groups. No epidemiologic studies of potential health effects in nonoccupational groups have been reported.

We have performed an epidemiologic study of residents in the Little Hocking water district in southeastern Ohio where there is significant environmental exposure to PFOA. Water supplied by the Little Hocking Water Association has been contaminated with PFOA for many years

he last 3 years at a mean level
μg/L. PFOA in the environ-
n the vicinity of Little Hocking
ierally believed to be coming
a neighboring industrial facility
; it is used as a solvent and
:sant for fluoropolymer produc-
We have shown that the resi-
of this water district have a
in serum (PFOA) that is ap-
mately 70 times that of the gen-
U.S. population and that the
r source of PFOA is water from
the public water supply or con-
iated residential well water (Em-
EA, Shofer FS, Zhang H, et al,
blished data). Serum (PFOA) was
nfluenced by age (higher in those
or ≥60), number of tap water
:s per day, number of weekly
ngs of home-grown fruits and
tables, and use of a carbon-based
ential water filter. Residents of the
who also worked in the produc-
area of the plant had the highest
A levels with residential and oc-
itional exposures appearing to be
tive.

i this article, we explore whether
ain biomarkers of toxicity and
:rse health effects, potentially at-
itable to PFOA based on animal
cologic studies, are associated
i serum (PFOA) in Little Hocking
er district residents. Specifically,
examine serum liver function tests,
lesterol, renal function tests, thy-
l-stimulating hormone (TSH), and
ious hematologic parameters. We
) examine whether studied indi-
uals reporting a previous clinical
gnosis of either liver or thyroid
ease have elevated PFOA com-
ed with study participants without
:h diagnoses.

iterials and Methods

lection and Study Group

The study group consisted of res-
:nts from a stratified random
mple of persons from households
io had resided in the Little Hock-
g Water Association district for at
ast 2 years supplemented by a
naller group of volunteers meeting the same eligibility criteria. The selection of households for the sampling frame, selection of the stratified random sample of residents, process for distributing invitations to participate, and participation rates are described elsewhere (Emmett EA, Shofer FS, Zhang H, et al, unpublished data). For our previous studies of routes of exposure, 18 residents, who had substantial occupationally exposed to PFOA in the production area of the fluoropolymer production facility, and had been selected into the study by chance through the stratified random sampling process were excluded from some analyses. These 18 subjects were all included in the analyses reported in this article.

Administration of Questionnaires

Administration of questionnaires and collection of blood samples were performed at the Grand Central Family Medicine Office in nearby Parkersburg, West Virginia. Informed consent was first obtained from each subject or parent or guardian in the case of minors. Minors under the ages of 17 were encouraged to give informed assent whenever feasible. Different questionnaires were administered to adults and children. Questionnaires were developed and revised after review by the members of the Community Advisory Committee and by a group of experts from the U.S. EPA. Before finalization, the questionnaires were pilot-tested on a representative group of 20 individuals from similar southeastern Ohio or western West Virginia communities who did not live in the Little Hocking Water Association District. Trained interviewers administered all questionnaires.

All adults 18 years and older were administered an adult questionnaire. The information elicited included demographic and occupational information, health conditions (ie, have you ever been treated for or told by a doctor that you have any of the following health conditions: cirrhosis of the liver, hepatitis, any other liver condition; hyperthyroidism, hyperactive or overactive thyroid, goiter or enlarged thyroid, hypothyroidism, or underactive thyroid; history of bleeding disorder, smoking, and alcohol habits?). All children were asked similar questions except that the questions about smoking and alcohol habits were omitted.

Blood and Samples

Phlebotomy was performed on all subjects. No subjects were given instructions to fast. Five milliliters of blood were taken into a purple-topped Vacutainer tube and sent for complete blood count (hemoglobin, hematocrit, red blood cell indices, white cell count and differential white cell count, platelet count). Thirty milliliters of blood were drawn into red-topped Vacutainer tubes: 10 mL were immediately sent for serum chemistry determinations (total protein, albumin, blood urea nitrogen, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase [SGOT], alanine aminotransferase [SGPT], gamma glutamyl transpeptidase [GGT], total cholesterol, TSH). Twenty milliliters of blood was immediately spun down and the serum frozen and stored pending shipping in batches to the Clinical Toxicology Laboratory at the University of Pennsylvania for PFOA analysis. The storage, shipping, and handling of samples and the assay procedure for PFOA are described elsewhere (Emmett EA, Zhang H, Shofer FS, et al, unpublished data). PFOA was analyzed using HPLC/tandem mass spectrometry by a modification of the method of Flaherty et al.[46]

Feedback of Results to Participants

Each participant was informed of his or her personal blood chemistry and hematologic results as well as PFOA together with any necessary explanation by a local healthcare provider (HZ or NR). Those few participants with markedly abnormal blood chemistry and/or hematologic results were personally telephoned by HZ or NR and the results dis-

cussed directly with the participant. Participants with abnormal laboratory results were advised to see their personal physician.

Statistical Analysis of Biomonitoring and Exposure Data

To determine if serum (PFOA) was correlated with any liver function or hematologic parameter, simple regression was used. To assess whether PFOA levels were increased in those with abnormal blood chemistries or hematologic values, binary groups were formed (normal vs abnormal) and tested using Student *t* test. Serum (PFOA) in participants with thyroid or liver disease was compared with those without disease using Student *t* test. For the regressions, data are presented using correlation coefficients and *P* values testing whether the slope of the line is 0. Serum (PFOA) is presented as mean, median, and interquartile range (IQR). All analyses were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). A $P < 0.05$ was considered statistically significant.

Human Subjects Approval

The study was approved by the Institutional Review Board of the University of Pennsylvania. Participation was voluntary. Informed consent was obtained for all participants before any study. A certificate of confidentiality was obtained from the National Institutes of Health to ensure maximum protection of personal information and results.

The study was conducted through a partnership among the University of Pennsylvania School of Medicine, the Decatur Community Association, a local community association in the Little Hocking water service area, and Grand Central Family Medicine in Parkersburg, West Virginia, a local healthcare provider, through a grant from the Environmental Justice Program of NIEHS. The community was involved at all stages of the study. The Community Advisory Committee included residents from the affected townships, representatives of the U.S. and Ohio Environmental Protection Agency, and the Health Commissioner for Washington County, Ohio.

Results

Demographics and Distribution of Serum (PFOA) in the Studied Population

Results were available from 371 individuals, 317 participants from the randomly selected sample and 54 from the volunteer group. Females represented 53.4% of the study sample ($N = 198$). The age distribution of the study group is presented in Table 1. The median age of the study group was 50 years (range, 2.5–89 years). There were 43 children under 18 years of age.

The distribution of serum (PFOA) in the studied individuals is presented in Figure 1. In the population, the median serum (PFOA) was 354 ng/mL and the interquartile range was 184 to 571 ng/mL. There was a fairly uniform distribution of values through approximately 450 ng/mL with a truncated distribution to around 2100 ng/mL and one value above 4000 ng/mL.

Relationship Between Serum (PFOA) and Chemistry and Hematologic Biomarkers

The mean, median, and interquartile range for the studied blood chemistry variables in this population are presented in Table 2. Additionally, we present a regression slope and correlation coefficient testing the relationship between serum (PFOA) and each blood or serum chemistry variable. No significant correlation between any test and PFOA was observed ($P > 0.05$ for

TABLE 1
Age Distribution of 371 Residents of Little Hocking Water Service District Participating in Study

Age (yrs)	Frequency	Percent	Cumulative Percent
2–10	20	5.39	5.39
11–20	29	7.82	13.21
21–30	20	5.39	18.60
31–40	42	11.32	29.92
41–50	80	21.56	51.48
51–60	93	25.07	76.55
>60	87	23.45	100.00
Total	371	100.00	

$N = 371$.

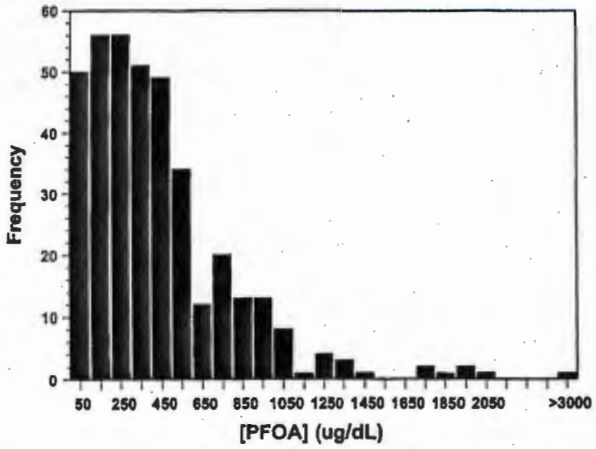

Fig. 1. Frequency distribution of serum (PFOA) in the studied population of residents of the Little Hocking water service district ($N = 371$).

ABLE 2
erum Chemistry Biomarkers in Study Population and Association With Serum (PFOA)

Liver Function Test	Mean	Standard Deviation	Median	Interquartile Range		Slope Estimate	r	P*
Blood urea nitrogen	14.97	5.32	14.0	12.0	18.0	0.0003657	0.028	0.59
Creatinine, serum	0.83	0.33	0.8	0.7	0.9	0.00000755	0.010	0.86
Protein, total, serum	7.18	0.38	7.2	6.9	7.4	0.00008149	0.087	0.10
Albumin, serum	4.32	0.27	4.3	4.1	4.5	0.00001197	0.017	0.74
Bilirubin, total	0.47	0.34	0.4	0.3	0.6	−0.00000467	0.000	0.92
Alkaline phosphatase, serum	101.50	70.99	82.0	67.0	101.0	−0.00416	0.024	0.65
Aspartate aminotransferase (SGOT)	23.94	19.53	21.0	18.0	27.0	−0.0007586	0.014	0.76
Aminotransferase (SGPT)	24.85	31.24	21.0	15.0	27.0	−0.00183	0.024	0.65
Gamma glutamyl transpeptidase	25.21	33.07	20.0	14.0	27.0	0.00057711	0.010	0.89
Cholesterol, total	198.01	38.86	194.0	172.0	220.0	0.00551	0.057	0.27
Thyroid-stimulating hormone	2.06	1.88	1.7	1.1	2.4	0.00021305	0.046	0.38

*Tests slope = 0.
N = 371.

ABLE 3
lematologic Variables in Study Population and Association With Serum (PFOA)

Hematologic Parameter	Mean	Standard Deviation	Median	Interquartile Range		Slope Estimate	r	P*
White blood cell count	6.89	1.79	6.8	5.5	7.9	0.00039608	0.09	0.08
Red blood cell count	4.55	0.41	4.5	4.3	4.8	0.00004031	0.04	0.44
Hemoglobin	13.95	1.27	13.9	13.0	15.0	0.00017275	0.06	0.29
Hematocrit	40.80	3.58	40.7	38.2	43.6	0.00039606	0.04	0.39
MCV	89.77	4.74	90.0	87.0	92.0	0.00020047	0.02	0.74
MCH	30.72	1.74	30.8	29.7	31.9	0.00014134	0.03	0.53
MCHC	34.21	0.67	34.3	33.8	34.7	0.00010286	0.06	0.23
RDW	13.38	1.09	13.2	12.6	13.9	−0.0001558	0.06	0.26
Platelets	256.80	60.61	248.0	218.0	285.0	0.00827	0.05	0.30
Neutrophils (%)	59.24	9.13	59.0	54.0	65.0	0.0004305	0.02	0.71
Lymphocytes (%)	30.98	8.20	31.0	25.0	36.0	−0.0006401	0.03	0.54
Monocytes (%)	6.39	2.36	6.0	5.0	8.0	0.00023119	0.04	0.44
Eosinophils (%)	3.01	2.20	2.0	2.0	4.0	−0.0000652	0.01	0.82
Basophils (%)	0.33	0.48	0.0	0.0	1.0	0.00003319	0.03	0.59
Neutrophils (absolute)	4.14	1.45	3.8	3.1	5.0	0.00025301	0.07	0.17
Lymphocytes (absolute)	2.10	0.70	2.0	1.6	2.5	0.00009406	0.05	0.29
Monocytes (absolute)	0.42	0.16	0.4	0.3	0.5	0.00005008	0.13	0.01
Eos (absolute)	0.21	0.16	0.2	0.1	0.2	0.00000252	0.00	0.90
Basos (absolute)	0.03	0.04	0.0	0.0	0.1	0.00000586	0.05	0.30

*Tests slope = 0.
N = 371.

all). This remained true whether the relationship was explored for all individuals a group or separately for adults aged 19 or older and children/adolescents aged 18 or less.

The mean, median, interquartile ranges, and the regression slope and correlation coefficient testing the relationship between serum (PFOA) and the studied hematologic variables are presented in Table 3. Only absolute monocyte count demonstrated a significant correlation with serum (PFOA) (P = 0.01). However, the slope estimate was small (slope = 0.00,005) and the correlation coefficient suggested a very weak positive correlation (r = .13). There was no significant relationship between serum (PFOA) and the percentage of monocytes in differential white cell counts.

We also evaluated whether the serum (PFOA) was significantly different between those with abnormal values for each of the serum chemistry and hematologic variables compared with those who had a normal value for that test. For this purpose, abnormal values were defined with respect to the normal ranges for the individual ages providing an additional check for age-related effects. Results for each variable were examined separately, as shown in Table 4. In three instances, AST (SGOT), percent neutrophils, and percent lymphocytes, there was a statistically significant difference (P = 0.03, 0.02, and 0.01, respectively). In each case, study individuals with abnormal values had lower serum (PFOA) compared with individuals with normal

TABLE 4
Comparison of Serum (PFOA) Between Those With Abnormal Values for Serum Chemistries and Hematologic Parameters and Those With Normal Values for That Parameter

Parameter	Abnormal	Abnormal Percent	*t* Test*
Blood urea nitrogen	6	2%	0.86
Creatinine, serum	17	5%	0.62
Protein, total, serum	2	0.5	ND
Albumin, serum	7	2%	0.83
Bilirubin, total	4	1%	0.70
Alkaline phosphatase, serum	6	2%	0.63
Aspartate aminotransferase (SGOT)	9	2%	0.03
Aminotransferase (SGPT)	28	8%	0.30
Gamma glutamyl transpeptidase	11	3%	0.50
Cholesterol, total	182	49%	0.79
Thyroid-stimulating hormone	24	6%	0.59
White blood cell count	18	5%	0.64
Red blood cell count	17	5%	0.18
Hemoglobin	16	4%	0.66
Hematocrit	2	0.5	ND
MCV	19	5%	0.43
MCH	18	5%	0.97
MCHC	0	0%	ND
RDW	25	7%	0.31
Platelets	8	2%	0.75
Neutrophils	35	9%	0.02
Lymphocytes	18	5%	0.01
Monocytes	39	11%	0.09
Eosinophils	19	5%	0.10
Basophils	0	0%	ND
Neutrophils (absolute)	12	3%	0.23
Lymphocytes (absolute)	3	1%	0.59
Monocytes (absolute)	7	2%	0.85
Eos (absolute)	22	6%	0.85
Basos (absolute)	0	0%	ND

*Tests for differences in PFOA values between normal and abnormal values.
$N = 371$.
ND indicates not determined.

values (AST: abnormal PFOA = 263 vs normal PFOA = 449; neutrophils: abnormal PFOA = 354 vs normal PFOA = 454; lymphocytes: abnormal PFOA = 327 vs norm PFOA = 450). In no instance was an abnormal value positively associated with PFOA.

Relationship Between Serum (PFOA) and Reported Liver or Thyroid Disease

Study individuals with liver disease ($N = 13$) had higher levels of PFOA (527 ng/mL) compared with individuals without liver disease (441 ng/mL) but this difference was not statistically significant ($P = 0.5$). Study individuals with thyroid disease ($N = 40$) had lower levels of PFOA (387 ng/mL) compared with individuals without thyroid disease (451 ng/mL), but this difference was also not statistically significant ($P = 0.3$).

Conclusions

We have found no significant positive association between serum (PFOA) and markers of a number of potential health effects from PFOA in a sample of residents from a community with markedly elevated serum (PFOA) compared with general population levels. The median serum (PFOA) in the studied residents was 354 ng/mL with an interquartile range of 184 to 571 ng/mL compared with a median serum (PFOA) in the general U.S. population of 4 to 5 ng/mL[5–7] and a median serum (PFOA) of 6 ng/mL (interquartile range, 5–10 ng/mL) in 30 Philadelphia area residents (Emmett EA, Shofer FS, Zhang H, et al, unpublished data). The median serum (PFOA) for 259 workers using PFOA at the fluoropolymer production facility neighboring the Little Hocking community was 490 ng/mL, and the median serum (PFOA) for 342 workers at that same facility who had never been assigned to PFOA areas was 110 ng/mL.[47]

The biomarkers for effect and the diseases were chosen on the basis of the known toxicity in experimental animals and the results of a limited number of human occupational studies.

Although PFOA has been described as binding with human and rat serum albumin,[48] we did not observe any association between serum (PFOA) and serum protein levels. We did not evaluate whether the concentration of PFOA was elevated in the protein compartment of serum compared with other compartments.

In rats, PFOA administration results in PPAR alpha activation and is associated with reduction in serum cholesterol levels.[1] The apparent association of increasing serum cholesterol with serum (PFOA) observed in three recent clinical studies of occupational groups is the opposite of what would be expected from PPAR alpha activation, suggesting a different mechanism in humans. In this study, we did not observe any association between serum (PFOA) and serum cholesterol.

In rodents, the liver appears to be the most sensitive target organ to the effects of PFOA. Subchronic and chronic toxicity studies show that PFOA administration produces increased liver size, diffuse hepatocellular hypertrophy and necrosis, and dose-dependent increases in serum alkaline phosphatase, ALT, and AST levels.[10,18] Male rats develop liver toxicity at lower levels than females perhaps reflecting slower elimination.[19] Not only is the liver the most sensitive organ in rats, but in rodent studies of PFOA administration, tumors have only been observed at PFOA dosages that result in overt

epatic damage, including changes ı ALT and AST. Therefore, the otential for adverse changes in bio-ıarkers of liver damage and any ssociation between higher serum PFOA) and past diagnosis or treat-ıent for liver disease in our study articipants were of particular inter-st. We observed no significant pos-ive associations between any of the udied biomarkers of potential liver xicity (serum albumin, total bilirubin, alkaline phosphatase, ALT, AST, GGT) with serum (PFOA), and no gnificant elevation of serum (PFOA) ı those with abnormal values for any f these biomarkers. Additionally, FOA was not significantly elevated ı those with a history of diagnosis or eatment of liver disease compared ith those with no history of liver isease. We concluded that PFOA was ot associated with demonstrable man-estations of increased liver disease in iis population.

We did not evaluate cancer out-omes and therefore can make no rm conclusions with regard to po-ntial carcinogenic outcomes in the udy population. Nevertheless, be-ause in rodents, cancer from PFOA ; always accompanied by evidence f frank liver damage, our failure to nd evidence of liver damage could quate to a low likelihood of cancer ıduction through nongenotoxic ıechanisms.

We did not find evidence for an ssociation of either blood urea nitro-en or serum creatinine and PFOA in ıe study population.

Reduced levels of thyroid hor-ıones have been observed both in ıonkeys fed PFOA[25] and in occupa-onally exposed groups as part of ıeir medical surveillance.[39] We ob-erved neither an association of se-ım (PFOA) with the levels of serum 'SH nor an increased serum (PFOA) ı those with a history of thyroid isease compared with those without uch disease. A history of thyroid isease was quite prevalent in this opulation, being reported by 11% of articipants, but we detected no contribution to this burden from PFOA exposure.

PFOA administration to monkeys is associated with bone marrow hypocellularity and there is evidence of immunotoxicity in both rats[21–23] and monkeys[19] fed PFOA. We did not observe changes in blood elements or in the differential white cell count associated with serum (PFOA). We consider that the isolated weak but statistically significant positive association of absolute monocyte counts and serum (PFOA) may have been a chance finding. This association has not been previously noted in published studies of those working with PFOA, and we observed no corresponding association between the percentage monocyte count and serum (PFOA).

Developmental and reproductive studies in rats fed PFOA have not demonstrated developmental defects in offspring[49] despite observed toxicity in parents. However, rat pup body weight was significantly reduced during lactation from PFOA-treated mothers. A two-generation reproductive study in rats found a slight but statistically significant: decrease in the lactation index for F1 male pups, increases in postlactation deaths in F1 females, delays in sexual maturation in F1 females, increase in estrous cycles in F1 females, and delay in sexual maturation in F1 males, which could have resulted from compromised nutritional status.[50] Thus, further investigation into potential reproductive and developmental effects of PFOA in humans is necessary.

We consider that our results would reflect the effects, if any, of long-term exposure to PFOA in this community setting. The plant considered the source of PFOA has been in operation since 1948 and has been involved in fluoropolymer production using PFOA since 1951. Contamination of the community water supply by PFOA was detected around 1984, although results were not publicly available until much later. PFOA levels in Little Hocking system water have been measured regularly for the past 3 years; there have been variations, but the levels have remained within a general range. Our study inclusion criteria included residence in the water system distribution area for at least 2 years before data collection. Thus, all participants would be expected to have had exposure to PFOA over a minimum period of 2 years.

The population we studied had serum (PFOA) very far above the mean PFOA observed to date in samples from the general U.S. population. Our failure to find an association between PFOA and the variables we studied makes it highly unlikely that these variables would be affected by the PFOA levels currently found in the general U.S. population. Our study did not address the possibility that PFOA might be contributing to other effects. Based on the findings in experimental animals, other end points, particularly cancer, reproductive and childhood development, require further study.

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